Primary aldosteronism (PA) is a common cause of hypertension; aldosterone excess is found in ≈10% of unselected hypertensives and up to 20% of subjects with resistant hypertension.1,2 Moreover, patients with PA demonstrate increased cardiovascular morbidity in comparison with subjects with equivalent essential hypertension (EH). In one study, where patients with PA were compared with matched hypertensives, PA patients demonstrated a 4-fold increase in stroke rate, 6.5-fold increase in risk of myocardial infarction, and 12-fold increase in the prevalence of atrial fibrillation. 3 Subsequent similar studies have confirmed these findings, implying that aldosterone excess has significant adverse cardiovascular effects beyond its influence on blood pressure (BP). 4–6

**Methods and Results**—Twenty-seven subjects with recently diagnosed PA and 54 essential hypertension controls were recruited. Subjects underwent gadolinium-enhanced cardiac magnetic resonance; noninfarct related myocardial fibrosis was identified by a diffuse pattern of late gadolinium enhancement. Patients also underwent assessment of pulse wave velocity, measurement of circulating superoxide anion and C-reactive protein, as well as blood pressure and biochemical assessment. Subjects were well matched with no difference in severity or duration of hypertension. There was a significant increase in the frequency of noninfarct late gadolinium enhancement in PA (70%) when compared with essential hypertension subjects (13%; *P*<0.0001) with no difference in left ventricular mass. Pulse wave velocity, superoxide, and C-reactive protein were significantly higher in subjects with PA.

**Conclusions**—These data illustrate that patients with PA exhibit frequent myocardial fibrosis as demonstrated by late gadolinium enhancement using cardiac magnetic resonance imaging; this finding is independent of blood pressure. This may be mediated partly through inflammation and oxidative stress. This study highlights the importance of specific targeting of aldosterone excess as well as blood pressure reduction to minimize cardiac morbidity in PA. (Circ Cardiovasc Imaging. 2012;5:740-747.)

**Key Words:** cardiac magnetic resonance imaging ■ fibrosis ■ primary aldosteronism ■ hypertension ■ aldosterone

In animal models of PA, cardiac fibrosis and hypertrophy occur independent of BP, as demonstrated by amelioration of these effects by nonantihypertensive doses of the mineralocorticoid receptor antagonist, spironolactone.7 However, the exact mechanism behind the deleterious cardiovascular effects of aldosterone remains unclear. There is strong evidence that aldosterone is proinflammatory, can directly stimulate cardiac fibroblasts, and can also increase vascular oxidative stress (by increasing availability of reactive oxygen species); these mechanisms can lead to scarring and fibrosis.8–10 In addition, aldosterone excess associates with increased arterial stiffness in both human and animal studies, which is reversed by mineralocorticoid receptor blockade. This may also contribute to cardiac structural changes. Finally, data have emerged supporting the role of...
intracellular calcium overload, in response to aldosterone-induced secondary hyperparathyroidism, in this process.11

The effect of aldosterone excess on cardiac structure and function in humans is unclear; some studies show no influence on left ventricular mass (LVM), whereas others suggest that PA associates with increased LVM compared with EH.12–15 However, most studies to date have assessed LV morphology using 2-dimensional echocardiography. Cardiac magnetic resonance (CMR) imaging offers a validated, precise, 3-dimensional measurement of LVM and morphology. It is becoming widely used in clinical practice for assessment of LV function and dimensions and for demonstration of evidence of prior ischemic heart disease.16,17 Furthermore, using gadolinium-based contrast agents, the presence of myocardial fibrosis can be implied by demonstrating the presence of late gadolinium enhancement (LGE). Contrast-enhanced CMR imaging has provided additional insights into conditions classically associated with fibrosis, such as myocardial infarction and hypertrophic, and dilated cardiomyopathy.17–19

The current study aimed to compare myocardial structure and composition in PA patients with matched EH using contrast-enhanced CMR to explore the key hypothesis that subjects with aldosterone excess were more likely to exhibit LGE suggestive of cardiac fibrosis. In addition, we aimed to provide some insight into the mechanistic basis of any differences by measuring noninvasive parameters of arterial stiffness as well as comparing common markers of inflammation and oxidative stress between patient populations.

Methods

Subjects

Twenty-seven subjects with confirmed PA diagnosed in the Western Infirmary, Glasgow were included. All were diagnosed with PA using Endocrine Society guidelines.20 Briefly, screened subjects with an elevated aldosterone to renin ratio (>750 with aldosterone in pmol/L and renin measured as plasma renin activity; >35 if renin measured as plasma renin concentration) underwent repeat screening after withdrawal of medications affecting measurements of plasma renin and aldosterone (for 4–6 weeks). If the elevated aldosterone to renin ratio persisted, then aldosterone excess was confirmed using a saline suppression test (PA confirmed if plasma aldosterone is >270 pmol/L despite infusion of 2 L of normal saline >4 hours). Subjects subsequently underwent adrenal imaging (computerized tomography) and adrenal vein sampling if appropriate to differentiate between unilateral and bilateral forms of PA. Importantly, all PA subjects included in the study were investigated either before or within 1 year of adrenalectomy or commencing specific medical therapy.

The control group comprised 53 EH subjects (2 per PA subject; except in 1 case where the control failed to complete the study) each matched to a PA subject for severity and duration of hypertension (established from casenote review), age, and sex. All such patients had a normal aldosterone to renin ratio and none were on mineralocorticoid receptor antagonists. No patient had pre-existing structural cardiac abnormalities (excluded by clinical examination and echocardiography where appropriate). All subjects were healthy out-patients with no intercurrent illness at the time of study.

Study subjects were evaluated in the morning after fasting from midnight. They underwent measurement of weight, height, and brachial BP (recorded as the average of triplicate measurements taken at intervals of 1 minute using a validated oscillometric device [HEM-907; Omron Healthcare, Kyoto, Japan] after an initial 5 minutes of seated rest). All bloods were measured after 30 minutes of supine rest.

This study was approved by the West of Scotland Research Ethics Committee and all subjects gave informed consent.

Cardiac MRI

Contrast-enhanced CMR was performed within 24 hours of the first study visit using a 1.5-Tesla Siemens Sonata (Siemens, Erlangen) with a phased-array chest coil, during breath-hold, and gated to the electrocardiogram. A steady-state free-precession sequence was used to acquire a short-axis cine stack of the LV from base to apex, consisting of 8-mm-thick slices with a 2-mm interslice gap. Ten minutes after the intravenous injection of a contrast agent (gadodate meglumine, Dotarem 0.1 mmol/kg; Guerbet, Roissy France) LGE images were acquired in the same views as for cine images, using a contrast-sensitive segmented inversion recovery sequence. The time to inversion was varied to obtain optimal nulling of the myocardium for the delayed enhancement sequences.

Postprocessing was performed using commercially available Argus software (Siemens, Erlangen). Manual planimetry, performed by 1 observer blinded to underlying diagnosis, was used to trace the epicardial and endocardial contours of each short-axis slice acquired in the cine stack, allowing calculation of LV volumes, LV ejection fraction, and LVM (myocardial density taken as 1.05 g/cm³). The most basal LV slice at both end-systole and end-diastole was defined as that in which the blood pool was surrounded by ≥50% of ventricular myocardium; papillary muscles were excluded from the LV volumes and included in the LVM.

LV systolic dysfunction was defined as LV ejection fraction <55%, with LV hypertrophy (LHV) defined as LVM index (LVMI) (LVM/body surface area; LVMI) >84.1 g/m² (male) or >76.4 g/m² (female) and LV dilation defined as end-diastolic volume/body surface area >111.7 mL/m² (male) or 99.3 mL/m² (female) or end-systolic volume >92.8 mL (male) or 70.3 mL (female) based on mean normal LV dimensions for healthy volunteers plus 2 SDs.21

Myocardial fibrosis was indicated by the presence of LGE as previously described with each image reviewed by 2 blinded independent observers. Images were assessed for the presence and pattern of gadolinium enhancement. Patients were classed as having positive LGE if LGE was seen on <2 (of 3) views: short-axis view, long-axis view, and reverse phase sequences, to exclude artifact. The pattern of LGE was defined as infarct (subendocardial) or noninfarct (diffuse).

Assessment of Arterial Hemodynamics

Carotid-femoral and carotid-radial pulse wave velocity (PWV) was carried out using the SphygmoCor Vx system (Atcor Medical, Sydney, Australia) by a single operator. PWV was measured from sequentially recorded electrocardiogram-gated carotid, radial, and femoral artery waveforms. The aortic augmentation index (AIx), a measure of wave reflection, was determined from radial waveforms sequentially recorded electrocardiogram-gated carotid, radial, and femoral artery waveforms. The aortic augmentation index (AIx), a measure of wave reflection, was determined from radial waveforms using the same device. The PWV and AIx measurements were made in triplicate, and the mean values were used in the subsequent analysis. Detailed descriptions of PWV and AIx measurements and their reproducibility have been reported previously.22

Plasma Measurements

Plasma renin activity was measured by the Biodata Renin MAIA (Seron Diagnostics Ltd, Woking, Surrey, United Kingdom) with an intraassay coefficient of variation (CV) <10% between 0.3 and 18 ng/mL-hours and a least detectable concentration of 0.3 ng/mL-hours. The interassay batch variation >1 year was 11% (quality control [QC] mean values, 2.3 and 6.1 ng/mL-hours). Plasma aldosterone was measured by direct radioimmunoassay utilizing the Coat-A-Count system (Euro/DPC Ltd, Caernarfon, Wales). The radioisotope used was 125I-aldosterone. CVs (%, within-batch and between-batch, respectively) were: 2.3 to 5.4 and 8.0 to 15.7.

In 2009, the local method of renin measurement changed to plasma renin concentration.23 This was measured using the Diasorin analyzer (Stillwater, MN) (normal range, 5–500 μIU/L). The intraassay CV was <3.4% and interassay CV was <6.2%. Oxidative stress status was assessed by analyzing superoxide release from whole blood,
using an established method. In brief, venous blood was collected in lithium heparinate containing tubes and processed immediately. Superoxide levels were detected by electron paramagnetic resonance (e-scan R; Bruker BioSpin GmbH, Rheinstetten, Germany) with the spin probe 1-hydroxy-3-carboxy-2,2,5,5-tetramethylpyrroline (CPH; Noxygen, Elzach, Germany) to a final concentration of 500 μmol/L. Instrument settings were as follows: center field, 3375 G; modulation amplitude, 2.27 G; sweep time, 5.24 seconds; sweep width, 60 G; and 10 scans. Superoxide levels were recorded as counts per minute for 10 minutes and a best fit regression line through these data points was constructed; the calculated slope of this line was used to measure the rate of superoxide anion production.

C-reactive protein was measured in a single run on all samples using a high-sensitivity method on a clinically validated automated platform (c311, Roche Diagnostics, Burgess Hill, United Kingdom). The analyzer was calibrated and quality controlled using the manufacturers’ reagents, and according to their instructions (CV <5%).

Statistics
Data were analyzed using SPSS (version 15 SPSS Inc, Chicago, IL) software. The matching of 2 EH subjects with each PA was accounted for by using these triplets as the clustering variable. Specifically, continuous variables were compared using a linear mixed effects model; nonnormally distributed variables underwent logarithmic transformation (log10) before analysis. The presence of myocardial fibrosis indicated by CMR was assessed using a General Estimating Equation model, with a logit link function.

Results
Clinical Characteristics
Table 1 summarizes the clinical details of PA subjects and their EH controls. Eleven patients with PA had adenomatous PA treated surgically; 7 were studied before adrenalectomy. Sixteen subjects had bilateral aldosterone excess (13 with bilateral adrenal hyperplasia, 3 with glucocorticoid remediable aldosteronism) treated medically; 3 were on no specific treatment for aldosterone excess at the time of study. The remaining subjects had commenced specific treatment or undergone adrenalectomy less than a year before the study date (mean time between initiation of definitive treatment was 147 days). Medically treated subjects were on spironolactone (n=8; mean dose 69 mg), eplerenone (n=3; mean dose 108 mg), or amiloride (n=1, dose 20 mg). Groups were well matched in terms of severity and duration of hypertension as well as age. patients with PA had a slightly higher body mass index than subjects with EH; this was unlikely to be of clinical significance. No subject in the EH group demonstrated an elevated aldosterone to renin ratio.

Cardiac Dimensions
Twenty-six patients with PA underwent CMR scanning (1 patient with PA was unable to tolerate magnetic resonance imaging [MRI]) along with 52 matched EH controls. Table 2 illustrates no significant difference in myocardial dimensions between subjects with PA and EH. Two patients in the EH group had LVH compared with 3 patients in the PA group. No patients with PA had LV systolic dysfunction with 1 patient with EH demonstrating mild LV systolic dysfunction.

Pulse Wave Velocity
Carotid-femoral and carotid-radial PWV were significantly higher in the PA group (Table 3). There was no significant difference in AIx between the 2 groups.

Presence of LGE
Gadolinium-enhanced CMR data were available for 24 patients with PA (1 not scanned, 2 refused gadolinium contrast). Of the 48 EH controls, 7 could not be analyzed for the presence of

Table 1. Summary of Clinical Characteristics of Patients With PA vs EH

<table>
<thead>
<tr>
<th></th>
<th>PA n=27</th>
<th>EH n=53</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>21 M/6 F</td>
<td>42 M/11 F</td>
<td>…</td>
</tr>
<tr>
<td>Age (y)</td>
<td>53.8 (11.2)</td>
<td>55.1 (9.4)</td>
<td>0.06</td>
</tr>
<tr>
<td>BMI, (kg/m²)</td>
<td>31.1 (5)</td>
<td>29.2 (4.6)</td>
<td>0.02</td>
</tr>
<tr>
<td>Serum potassium (mmol/L)</td>
<td>3.4 (0.5)</td>
<td>3.9 (0.4)</td>
<td>0.01</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)</td>
<td>110.1 (26.8)</td>
<td>116.1 (33.9)</td>
<td>0.5</td>
</tr>
<tr>
<td>Plasma aldosterone (pmol/L)</td>
<td>754 (299)</td>
<td>260 (208)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ARR</td>
<td>1998 (975)</td>
<td>1536 (145.8)</td>
<td>13.78 (31.31)</td>
</tr>
<tr>
<td>Urine sodium (mmol/24h)</td>
<td>173.8 (88.7)</td>
<td>176.4 (82.4)</td>
<td>0.71</td>
</tr>
<tr>
<td>Urine potassium (mmol/24h)</td>
<td>76.1 (29.3)</td>
<td>89.2 (29)</td>
<td>0.09</td>
</tr>
<tr>
<td>Urine albumin (mg/24h)</td>
<td>110 (131)</td>
<td>43.9 (71.4)</td>
<td>0.14</td>
</tr>
<tr>
<td>Urine albumin: creatinine</td>
<td>6.33 (7.9)</td>
<td>14.4 (11.7)</td>
<td>0.92</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>150.3 (26.6)</td>
<td>152.63 (19.3)</td>
<td>0.65</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>89.9 (11.9)</td>
<td>94.3 (11.2)</td>
<td>0.12</td>
</tr>
<tr>
<td>Number of antihypertensive medications</td>
<td>2.5 (1.6)</td>
<td>2.2 (1.4)</td>
<td>0.37</td>
</tr>
<tr>
<td>Duration of hypertension (y)</td>
<td>9.2 (8)</td>
<td>11.3 (8.3)</td>
<td>0.84</td>
</tr>
</tbody>
</table>

PA indicates primary aldosterone; EH, essential hypertension; ARR, aldosterone to renin ratio; BMI, body mass index; SBP, systolic blood pressure; PRA, plasma renin activity; PRC, plasma renin concentration; and DBP, diastolic blood pressure.

Data are means (± SD). Data compared by linear mixed effects model.

*ARR expressed using PRA (normal range < 750 pmol/L/µg/mL/h).
†ARR expressed using PRC (normal range < 35 pmol/L/µIU/mL).
LGE because of breathing artifact, meaning 7 patients with PA had only one matched EH control.

One patient with PA demonstrated an infarct pattern on LGE; this patient had a previous anterior myocardial infarction several years earlier. Two subjects with EH demonstrated LGE pattern suggestive of previous myocardial infarction. Once the analysis was unblinded, it was shown that 1 patient had pre-existing coronary artery disease. The other patient had no such personal history and was referred for cardiac follow up. These subjects were excluded from subsequent analysis.

Figure 1 gives typical long-axis and basal/mid-cavity/apical short-axis views of noninfarct LGE in subjects with PA (Figure 1C and 1D), as well as a subject with PA and EH with no LGE for comparison (Figure 1A and 1B, respectively). The frequency of noninfarct LGE was significantly higher in the PA group (16/23; 70%) compared with EH subjects (5/39; 13%), P<0.0001 (Figure 2).

The presence of LGE was independent of BP and myocardial mass with no significant difference in these parameters in subjects (either PA or EH) with LGE when compared with those without LGE.

**Adenomatous Versus Bilateral PA**

PA subjects underwent further analysis to determine whether cause of aldosterone excess affected cardiac outcomes. There was no significant difference in the frequency of LGE between subgroups—73% (8/11) of adenomatous PA demonstrated LGE compared with 69% (9/13) of patients with bilateral aldosterone excess (P=0.6). Similarly, there was no significant difference in mean BP, age, myocardial mass, or LVMI between subgroups.

**Table 2. Summary of Cardiac Dimensions of Patients With PA vs EH as Analyzed by Cardiac MRI**

<table>
<thead>
<tr>
<th>Variable</th>
<th>PA</th>
<th>EH</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF (%)</td>
<td>77 (6)</td>
<td>70 (10)</td>
<td>0.002</td>
</tr>
<tr>
<td>LV EDV (mL)</td>
<td>123 (27)</td>
<td>132 (31)</td>
<td>0.2</td>
</tr>
<tr>
<td>SV (mL)</td>
<td>94 (20)</td>
<td>91 (22)</td>
<td>0.6</td>
</tr>
<tr>
<td>LVM (g)</td>
<td>135 (34)</td>
<td>128 (33)</td>
<td>0.2</td>
</tr>
<tr>
<td>LVMi (g/m²)</td>
<td>64 (13)</td>
<td>62 (13)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

PA indicates primary aldosterone; EH, essential hypertension; EF, ejection fraction; LVEDV, left ventricular end-diastolic volume, SV, stroke volume, LVM, left ventricular mass; MRI, magnetic resonance imaging; and LVMI, left ventricular mass index.

Data are means (±SD) compared by linear mixed effects model.

**Plasma Markers**

Whole blood superoxide levels were significantly higher in patients with PA compared with EH subjects (Figure 3). Plasma C-reactive protein levels were also significantly higher in patients with PA (Figure 4).

**Discussion**

These data illustrate that subjects with PA are significantly more likely to exhibit myocardial fibrosis (as demonstrated by noninfarct pattern of LGE) when compared with subjects with equivalent EH. Additionally, this phenomenon may be partly mediated by oxidative stress and inflammation given the significantly higher levels of whole blood superoxide and C-reactive protein found in subjects with PA in comparison with EH. These data are the first, to our knowledge, to demonstrate the presence of BP-independent myocardial fibrosis using gadolinium-contrast CMR in humans with PA and support the concept that targeting of aldosterone excess in addition to lowering BP are equally important in this patient group.

The results from this study confirm previous animal studies which demonstrated that aldosterone can cause cardiac fibrosis independent of its effect on BP or on the development of ventricular hypertrophy.26,27 Crucially, these profibrotic actions of aldosterone only develop in animals fed a high salt diet.28 Mean urinary sodium excretion did not differ significantly between the 2 patient groups we studied, but the mean excretion rate in both indicates that our patients were consuming a salt-rich diet characteristic of our local population. We speculate that this feature is likely to exacerbate the deleterious effects of aldosterone excess in our study.

Regional myocardial fibrosis is well described using delayed gadolinium-contrast enhancement during cardiac MRI.29 Areas of myocardial damage and collagen deposition have a much slower washout rate of gadolinium-based contrast than healthy myocardium, leading to a markedly increased signal intensity on T1-weighted imaging.30 This phenomenon of LGE is well established in ischemic heart disease which associates with discrete areas of LGE typically within the subendocardium.30 Recently, we have described a diffuse pattern of LGE in patients without coronary artery disease, which probably represents less severe myocardial fibrosis or milder degrees of excess collagen deposition.31 While LGE cannot be used synonymously for fibrosis without cardiac biopsy data, there was no evidence of other possible causes (myocarditis, interstitial amyloid) within our patient groups supporting our conclusion that diffuse LGE in these subjects was a consequence of aldosterone-driven myocardial fibrosis. These results confirm and extend earlier studies by Rossi et al32 who, using echocardiography and videodensitometry, demonstrated alterations in myocardial textures consistent with increased collagen deposition in PA and not EH subjects.

Noninfarct LGE was found in only 13% of our subjects with EH. This proportion may seem lower than expected; a recent study by Rudolph et al33 demonstrated LGE in 50% of subjects with EH. However, these subjects had CMR evidence of global LVH and were preselected by the presence...
of LVH on echocardiography, implying more significant underlying hypertension with the expectation of more significant cardiac structural abnormalities. In contrast, LVH was only demonstrated in 2 of our subjects with EH. The presence of cardiac fibrosis without LVH is reminiscent of the original experiments of Karl Weber and colleagues. In rodents with renovascular or aldosterone/salt induced hypertension fibrosis was seen not only of the hypertrophied left ventricle, but also of the normotensive, nonhypertrophied left ventricle. The

Figure 1. Horizontal long-axis (i) and basal/mid-cavity/apical short-axis views (ii–iv) of contrast-enhanced cardiac MRI images of (A) EH subject (no LGE); (B) PA subject (no LGE); (C) PA subject (noninfarct LGE in images i and ii). D. PA subject (localized noninfarct LGE in images i–iii). EH indicates essential hypertension; PA, primary aldosteronism; LGE, late gadolinium enhancement; and MRI, magnetic resonance imaging.

Figure 2. Frequency of noninfarct late gadolinium enhancement in primary aldosterone (PA) vs essential hypertension (EH) patients. Frequencies compared using logistic regression (general estimating equations). Subjects with late gadolinium enhancement because of myocardial infarction were excluded.

Figure 3. Whole blood superoxide levels in primary aldosterone (PA) patients compared with matched essential hypertension (EH). Rate of production is derived from the gradient of the regression line drawn between 10 data points for each sample (full details in methods section). Logarithmic transformed data (log10) were compared using linear mixed effects model.
right ventricle, implying that fibrosis can occur because of humoral (ie, aldosterone) rather than hemodynamic factors.

PWV was significantly higher in patients with PA versus EH, implying increased arterial stiffness in this group. These results confirm previous similar data as well as findings of Rizzoni et al, who demonstrated increased total and type III vascular collagen in the extracellular matrix of small resistance arteries in PA and matched EH patients. There was no difference in AIX between groups. The reasons for this are speculative but may reflect the relatively young age of our cohort; it has been postulated that, because pulse pressure only increases significantly after the fifth decade, stiffening of the large arteries tends to occur in later life.

Previously, the effect of aldosterone excess on LVH in humans has been controversial. In a separate study, Rossi et al showed, using echocardiography, that LV wall thickness and LVM were increased in PA subjects; this finding was also demonstrated by other investigators. However, other groups have shown no difference in LV dimensions between PA and EH subjects. Our data show no significant difference in LVM or LVMI between patients with PA and EH. This may reflect relatively mild hypertension demonstrated by the patients with PA in this study. Additionally, most other studies of LV dimensions in PA and hypertensive patients rely on echocardiography data; cardiac MRI provides a more sensitive method of structural analysis, and it is unclear how well MRI and echocardiographic findings correlate. In the previously quoted study by Rudolph et al, LVH using CMR was found in only 83 of 440 subjects (18%) with pre-identified LVH using echocardiography. It is pertinent that, in the only other study relating aldosterone status with CMR findings, there was no significant difference in LVMI between EH subjects with high versus low aldosterone production. Patients with PA did demonstrate an increased ejection fraction when compared with EH subjects. This may reflect the volume-expanded status of patients with mineralocorticoid excess. In an analogous situation, subjects with PA demonstrate increased estimated glomerular filtration rate in comparison with EH (suggestive of early glomerular hyperfiltration) and this resolves with treatment of aldosterone excess.

Numerous human and animal studies demonstrate that aldosterone increases proinflammatory cells and cytokines leading to vascular inflammation and fibrosis. In addition, chronic aldosterone and salt treatment in rats increases the expression of nicotinamide adenine dinucleotide phosphate oxidase in the myocardium which catalyses the formation of the superoxide anion which, in turn, promotes inflammation and fibrosis. All of these effects are attenuated by the administration of mineralocorticoid receptor antagonists and so suggest that aldosterone induces a proinflammatory phenotype, at least in part by increasing oxidative stress. This is supported by our finding of significantly elevated levels of the inflammatory hormone C-reactive protein, as well as whole blood superoxide in subjects with PA when compared with EH. Recently, there has been evidence in rats with aldosterone excess that oxidative stress and cardiac fibrosis may occur as a consequence of intracellular cardiac calcium overload. Human and animal studies suggest that PA is accompanied by mild secondary hyperparathyroidism and resultant intracellular calcium overload in response to excess urinary and fecal loss of calcium and magnesium. Although we did not measure serum parathyroid hormone in our study, mean serum adjusted calcium was significantly lower in patients with PA (2.37 mmol/L versus 2.47 mmol/L \( P<0.006 \)), which supports this intriguing hypothesis.

Strengths of this study include the rigorous matching of newly diagnosed PA patients to subjects with EH, as well as the use of the gold standard technique of CMRI as a noninvasive tool to accurately assess cardiac dimensions and gadolinium enhancement patterns characteristic of noninfarct related fibrosis.

Although subjects with PA were studied as close to diagnosis as possible and always within a year of diagnosis/initiation of treatment, it could be that some subjects demonstrated rapid regression of LVH in response to medical or surgical management of aldosterone excess and this is a potential weakness of the study. In the studies of Catena et al, where a large cohort of patients with PA were followed up for a mean of 7 years after medical or surgical therapy, there was a significant reduction in LVMI in PA within a year of surgical (although not medical) management despite similar reductions in BP. In our cohort, however, the mean time between initiation of specific treatment of aldosterone excess and study visit was <5 months, and so it is unlikely that any substantial cardiac benefit would have been evident. Moreover, a small number of patients with PA (n=10) were studied before treatment of aldosterone excess. There was no significant difference in the frequency of LGE in this cohort when compared with the treated PA group (frequency of 56% and 67%, respectively, \( P>0.05; \) data not shown). In addition, there was evidence of increased inflammation, oxidative stress, and increased vascular stiffness in the PA group, supporting the theory that aldosterone excess was still exerting adverse effects. Indeed, the significantly positive findings of this study, despite the inclusion of recently treated PA subjects, may imply that the results would have been more striking if untreated patients had been studied and suggests that these results in fact represent a conservative summary of the adverse cardiovascular effects of aldosterone.

In conclusion, we have demonstrated for the first time that subjects with PA are more likely to develop cardiac fibrosis.
as evidenced by a noninfarct pattern of diffuse LGE on cardiac MRI, than matched subjects with EH. We have further shown that myocardial fibrosis in these subjects may be partly mediated by proinflammatory and oxidative stress effects of aldosterone excess. These data highlight that amelioration of aldosterone excess by specific medical or surgical measures in addition to BP reduction is crucial in this common patient cohort.

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Disclosures

None.

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**CLINICAL PERSPECTIVE**

It was previously thought that primary aldosteronism represented a rare and fairly benign form of hypertension. However, it is now clear that primary aldosteronism is a common cause of hypertension and associates with excess cardiac morbidity, independent of blood pressure effects. Until recently, imaging modalities to demonstrate aldosterone-mediated cardiac fibrosis have been inferred by using 2-dimensional echocardiography and videodensitometry, as well as measuring plasma markers of collagen turnover. The current study is the first to use contrast-enhanced cardiac magnetic resonance imaging, the gold standard imaging technique for myocardial fibrosis, to demonstrate the effects of aldosterone excess in subjects with no evidence of coronary artery disease. Our data provide further evidence that myocardial fibrosis can occur due to aldosterone-mediated cardiac damage that is independent of blood pressure. These results highlight the importance of early diagnosis of this condition in subjects with high blood pressure. They suggest that treatment strategies should be aimed at ameliorating the effects of aldosterone excess as well as lowering blood pressure. Whether aldosterone-mediated cardiac fibrosis is reversible with treatment of aldosterone excess remains to be seen.
Demonstration of Blood Pressure-Independent Noninfarct Myocardial Fibrosis in Primary Aldosteronism: A Cardiac Magnetic Resonance Imaging Study

E. Marie Freel, Patrick B. Mark, Robin A.P. Weir, Emily P. McQuarrie, Karen Allan, Henry J. Dargie, John D. McClure, Alan G. Jardine, Eleanor Davies and John M.C. Connell

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